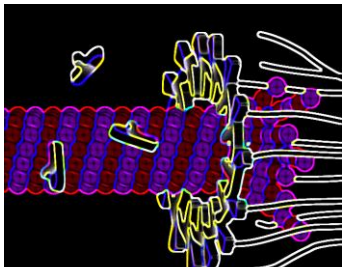
Life Sciences Division

E-Newsletter October 29, 2007

Highlights

Microtubule and kinetochore, engage!



Central to the essential process of chromosome segregation is the dynamic interaction between microtubules and kinetochores. A standing question in cell biology is how this dynamic attachment is maintained, especially during anaphase, when the microtubule ends interacting with the kinetochore are breaking apart. In budding yeast the kinetochore Dam1 complex self-assembles into a ring structure around the microtubule that then is able to travel processively with the depolymerizing end. The Nogales lab in the Life Sciences Division, in collaboration with Profs. Barnes and Drubin at UC Berkeley, has now structurally characterized this complex, both before and after engaging a microtubule, using electron microscopy and image reconstruction. They have found that a conformational change in the Dam1 complex accompanies its interaction with the microtubule and the formation of the ring, and thus prevents premature assembly that will require threading of the microtubule. The translocation of the ring powered by the peeling of microtubules is possible thanks to the special character of the interaction between the Dam1 complex and the microtubule involving long, flexible regions in the tubulin subunit.

Dr. Eva Nogales is a Howard Hughes Medical Institute investigator; a Professor of Biochemistry and Molecular Biology at the University of California, Berkeley; and Staff Scientist at the Lawrence Berkeley National Laboratory.

Link to the paper:http://www.nature.com/nsmb/journal/v14/n8/abs/nsmb1274.html
Link to Lynn Yarris write up:
http://www.lbl.gov/Science-Articles/Archive/sabl/2007/Oct/onering.html

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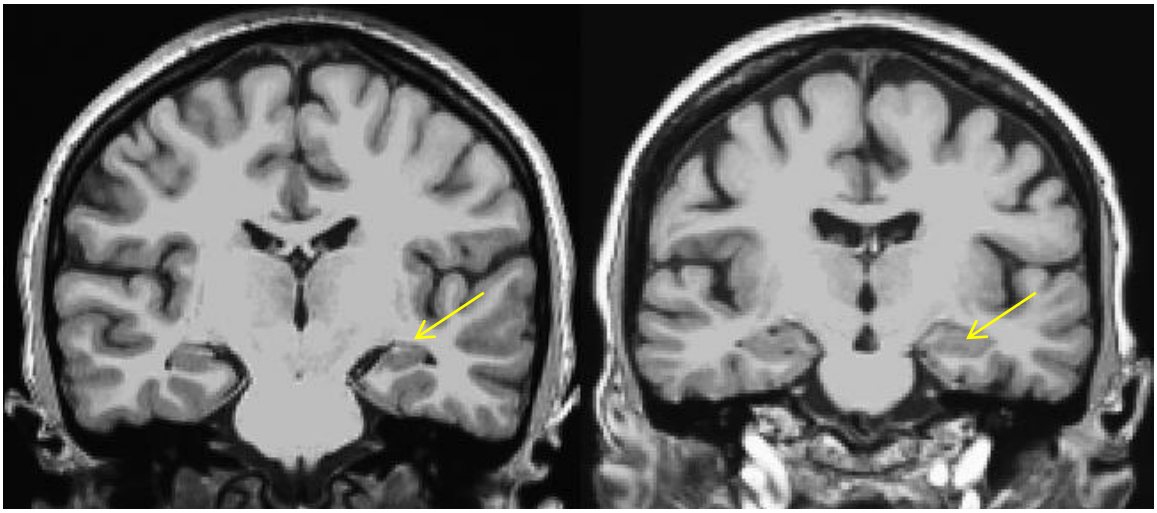
New MR Imaging System Installed

In April 2007 LBNL took delivery of a new 1.5 Tesla Siemens Avanto MR imaging system. The magnet was installed in Building 55A and became operational after a month of testing. For the past 5 months, investigators in the Department of Molecular Imaging and Neuroscience have been using the instrument to obtain high quality structural MRs of research subjects, and they are currently finalizing the hardware and software modifications necessary to obtain functional MR images as well.

The instrument will be invaluable in many ongoing research protocols. Structural images are a key part of interpreting the molecular images of such processes as brain chemistry and physiology that are obtained with PET scanning. These images are used to help localize the distribution of radiotracers in the brain, correct PET images for age-associated atrophy, and define the changes in brain structure that occur with a range of age-related and disease-related processes. The ability to perform functional MR scans will allow investigators to understand how changes in brain biochemistry are associated with changes in brain activity.

The images below are typical of those obtained on the scanner. They show, in exquisite detail, grey and white matter and several structures including the hippocampus (arrows), a structure in the brain that is important for memory and which is particularly susceptible to age-related decline.



By

William Jagust

The Jagust Lab is a joint research program involving the UC Berkeley Helen Wills Neuroscience Institute, UC Berkeley School of Public Health, and the Lawrence Berkeley National Laboratory (LBNL). At LBNL, neuroscientists, radiochemists, physicists, engineers and computer scientists work together to develop and refine imaging techniques. The imaging facility at LBNL includes a PET, SPECT and 1.5T MRI.

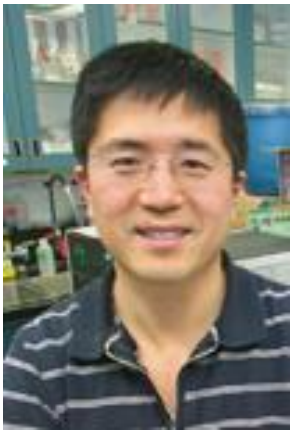
Spotting Alzheimer's Before Symptoms

Effective treatments for Alzheimer's disease appear several years away but, in what could be considered a painful irony, scientists have become increasingly adept at spotting the illness in its earliest stages. "Even since five years ago, there's been a huge technical jump," says Berkeley Lab life scientist **William Jagust**. "I think, for the first time, we have the idea that we might be able to predict what happens to normal older people who aren't having symptoms — to predict who among that group is destined to develop Alzheimer's disease could be possible. "

For more information go to:
http://www.latimes.com/features/health/la-he-lab8oct08,1,6984831.story

Today at Berkeley Lab October 9, 2007

China Plans Largest Ever Genetic Bank



With China's National Day holidays out of the way, students in Taizhou, Jiangsu, are returning to their voluntary duties of collecting genetic data from the city's willing citizens. Volunteers and sample donors will contribute to what project organizers claim could become the world's largest genetic databank. Genetic testing provides "personalized" medicine or the ability to "predict a response to a drug, either positive or negative, depending on genetic background," explains **Fanqing Chen**, Berkeley Lab life scientist and adviser to the project.

For the full story:
http://news.bbc.co.uk/1/hi/sci/tech/7046586.stm

Today at Berkeley Lab October 19, 2007

Department of Defense Innovator Award

The Department of Defense has notified **Joe Gray**, Director of the Life Sciences Division, that his proposal for "Early Detection of Metastasis-Prone Breast Cancers"

will receive an Innovator Award from DOD's Breast Cancer Research Program, the world's second-largest funding agency for breast cancer research. Gray's proposal lays out a plan for detecting breast cancers before they metastasize, greatly improving chances of survival. Anatomic detection using MRI and PET imaging will target metastasis-prone subtypes. Scanning tissue sections using mass-spectrometry imaging will result in better histopathological methods. This five year award will support the activities of a multi-disciplinary team to develop molecular imaging strategies to localize metastasis prone breast cancer before it has had time to spread – an area where conventional mammography is weak. This project brings together scientists with expertise in nuclear medicine, systems biology, chemistry and biochemistry

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Predictive Markers in Breast Cancer

A team of scientists at LBNL and UC San Francisco including **Joe Gray, Paul Spellman, Bahram Parvin**, **Mina Bissell, Paul Yaswen** and **Mary Helen Barcellos Hoff** in the Life Sciences Division have described molecular markers that identify breast cancer patients that are not likely to respond to current therapeutic strategies. They also developed a biological system to identify experimental drugs and drug combinations that will be effective in treating these resistant patient subpopulations. This project is funded by the NCI Integrative Cancer Biology Program and a growing consortium of pharmaceutical and biotechnology companies.

The Cancer Genome Atlas (TCGA) Project

LBNL scientists **Joe Gray** and **Paul Spellman** are leading a LBNL and UC Berkeley team that is participating in a national effort funded by the NCI and NHGRI to apply large scale genome characterization and sequencing technologies to define a "parts list" of molecular abnormalities that contribute to the pathophysiology of cancer. Initial efforts are focusing on glioblastoma, ovarian cancer and lung cancer.

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siRNA Therapy Consortium

Joe Gray at LBNL and **Steve Martin** at UC Berkeley are heading a multi-institutional consortium whose goal is to develop siRNA-based therapeutic agents to treat human cancers. Research in this postdoctopral fellow driven consortium focuses on the biology of siRNA processing, identification of targets that can be effectively attacked using siRNAs and siRNA delivery technologies. Participating institutions include LBNL, UC Berkeley, UC San Francisco, UC San Diego, and the MD Anderson Cancer Center.

IEEE Nuclear Science Symposium, Honolulu, Hawaii

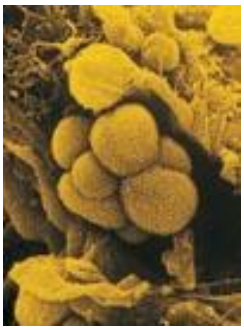
LBNL will be presenting at this year's annual IEEE Nuclear Science Symposium, October 26-November 3, the first scintillator radiation detector material that was predicted by theoretical calculation. Andrew Canning of the Computational Research Division will present a paper on the development and validation of computational methods for predicting cerium-activated scintillators and the use of these methods to predict that Ba2YCl7: Ce would be a good scintillator. Edith Bourret of the Materials Sciences Division will be presenting a paper on the experimental verification that this is in fact a new, bright scintillator material. This work was funded by the Department of Homeland Security and is a collaboration between LSD, MSD, and CRD.

Authors on these two papers include:
Life Sciences Division: **Stephen Hanrahan, Yetta Porter-Chapman, Scott Taylor, Rostyslav Boutchko, Marvin Weber, and Stephen Derenzo**
Materials Sciences Division: E.D. Bourret-Courchesne
Computational Research Division: Andrew Canning, Rostyslav Boutchko, and Lin-Wang Wang

For more information go to: http://www.nss-mic.org/2007/

By Stephen Derenzo

MSRI - ICBP



A workshop focusing on the application of mathematical and computational tools to understand the properties of cancer and other biological systems was held at the Mathematical Sciences Research Institute in Berkeley October 24-26. The workshop was designed to encourage and support the mathematical community's involvement in the effort to study cancer using systems approaches. This workshop was co-sponsored by the Lawrence Berkeley National Laboratory and SRI International. Conference presenters included mathematicians and computer scientists presently involved in systems approaches to cancer and more general fields of biology. Presentations covered general approaches to systems biology including analysis of genome scale data as well as statistical, continuous, and hybrid methods for pathway modeling. From a biological perspective, the workshop capitalized on work being performed by Investigators at LBNL, SRI, and UCSF who study the signaling networks associated with breast cancer. The program is developing high throughput assays to characterize these cell lines and examine how they respond to manipulations of key genes. Assays included mRNA expression profiling, measurements of protein abundance, and phenotypic responses using high content screening microscopy. Data and models from this program were shared at the workshop (prior to publication) for examination and analysis by the participants.

Today at Berkeley Lab October 8, 2007

Recent publications (selected)

Andreeva, L.S., N.I. Pechurkina, O.V. Morozova, E.I. Ryabchikova, S.I. Belikov, L.I. Puchkova, E.K. Emelyanova, ***T. Torok***, and V.E. Repin 2007. */Roseomonas baikalica/* sp. nov., a new bacterial species isolated from core samples collected by deep-hole drilling at the bottom of Lake Baikal. Microbiology 76:1-8.

> Considerable numbers of novel previously undescribed microbial species were isolated from sub-bottom sedimentary rocks representing different times in the geological history of the Lake Baikal Rift. Present study is devoted to the description and identification of strain ?he 82. This new bacterial species was determined to belong to the class */Alphaproteobacteria/*, the family */Methylobacteriaceae/*, and the genus */Roseomonas/*. The new species was named */R. baikalica/* sp. nov.

Rodier F, **Campisi J,** Bhaumik D. Nucleic Acids Res Two faces of p53: aging and tumor suppression 2007 Oct 16; [Epub ahead of print] PMID: 17942417

> The p53 tumor suppressor protein, often termed guardian of the genome, integrates diverse physiological signals in mammalian cells. In response to stress signals, perhaps the best studied of which is the response to DNA damage, p53 becomes functionally active and triggers either a transient cell cycle arrest, cell death (apoptosis) or permanent cell cycle arrest (cellular senescence). Both apoptosis and cellular senescence are potent tumor suppressor mechanisms that irreversibly prevent damaged cells from undergoing neoplastic transformation. However, both processes can also deplete renewable tissues of proliferation-competent progenitor or stem cells. Such depletion, in turn, can compromise the structure and function of tissues, which is a hallmark of aging. Moreover, whereas apoptotic cells are by definition eliminated from tissues, senescent cells can persist, acquire altered functions, and thus alter tissue microenvironments in ways that can promote both cancer and aging phenotypes. Recent evidence suggests that increased p53 activity can, at least under some circumstances, promote organismal aging. Here, we discuss the role of p53 as a key regulator of the DNA damage responses, and discuss how p53 integrates the outcome of the DNA damage response to optimally balance tumor suppression and longevity.

Guan Y, Kuo WL, Stilwell JL, Takano H, L**apuk AV**, Fridlyand J, Mao JH, Yu M, Miller MA, Santos JL, Kalloger SE, Carlson JW, Ginzinger DG, **Celniker SE**, Mills GB, Huntsman DG, **Gray JW**. Amplification of PVT1 Contributes to the Pathophysiology of Ovarian and Breast Cancer Clin Cancer Res. 2007 Oct 1;13(19):5745-55 PMID: 17908964

> PURPOSE: This study was designed to elucidate the role of amplification at 8q24 in the pathophysiology of ovarian and breast cancer because increased copy number at this locus is one of the most frequent genomic abnormalities in these cancers. EXPERIMENTAL DESIGN: To accomplish this, we assessed the association of amplification at 8q24 with outcome in ovarian cancers using fluorescence in situ hybridization to tissue microarrays and measured responses of ovarian and breast cancer cell lines to specific small interfering RNAs against the oncogene

MYC and a putative noncoding RNA, PVT1, both of which map to 8q24. RESULTS: Amplification of 8q24 was associated with significantly reduced survival duration. In addition, small interfering RNA-mediated reduction in either PVT1 or MYC expression inhibited proliferation in breast and ovarian cancer cell lines in which they were both amplified and over expressed but not in lines in which they were not amplified/over expressed. Inhibition of PVT1 expression also induced a strong apoptotic response in cell lines in which it was over expressed but not in lines in which it was not amplified/over expressed. Inhibition of MYC, on the other hand, did not induce an apoptotic response in cell lines in which MYC was amplified and over expressed. CONCLUSIONS: These results suggest that MYC and PVT1 contribute independently to ovarian and breast pathogenesis when over expressed because of genomic abnormalities. They also suggest that PVT1-mediated inhibition of apoptosis may explain why amplification of 8q24 is associated with reduced survival duration in patients treated with agents that act through apoptotic mechanisms.

Guipponi M, Toh MY, Tan J, Park D, Hanson K, Ballana E, Kwong D, Cannon PZ, Wu Q, Gout A, Delorenzi M, **Speed TP**, Smith RJ, Dahl HH, Petersen M, Teasdale RD, Estivill X, Park WJ, Scott HS. An integrated genetic and functional analysis of the role of type II transmembrane serine proteases (TMPRSSs) in hearing loss Hum Mutat. 2007 Oct 5; PMID: 17918732

Building on our discovery that mutations in the transmembrane serine protease, TMPRSS3, cause nonsyndromic deafness, we have investigated the contribution of other TMPRSS family members to the auditory function. To identify which of the 16 known TMPRSS genes had a strong likelihood of involvement in hearing function, three types of biological evidence were examined: 1) expression in inner ear tissues; 2) location in a genomic interval that contains a yet unidentified gene for deafness; and 3) evaluation of hearing status of any available Tmprss knockout mouse strains. This analysis demonstrated that, besides TMPRSS3, another TMPRSS gene was essential for hearing and, indeed, mice deficient for Hepsin (Hpn) also known as Tmprss1 exhibited profound hearing loss. In addition, TMPRSS2, TMPRSS5, and CORIN, also named TMPRSS10, showed strong likelihood of involvement based on their inner ear expression and mapping position within deafness loci PKSR7, DFNB24, and DFNB25, respectively. These four TMPRSS genes were then screened for mutations in affected members of the DFNB24 and DFNB25 deafness families, and in a cohort of 362 sporadic deaf cases. This large mutation screen revealed numerous novel sequence variations including three potential pathogenic mutations in the TMPRSS5 gene. The mutant forms of TMPRSS5 showed reduced or absent proteolytic activity. Subsequently, TMPRSS genes with evidence of involvement in deafness were further characterized, and their sites of expression were determined. Tmprss1, 3, and 5 proteins were detected in spiral ganglion neurons. Tmprss3 was also present in the organ of Corti. TMPRSS1 and 3 proteins appeared stably anchored to the endoplasmic reticulum membranes, whereas TMPRSS5 was also detected at the plasma membrane. Collectively, these results provide evidence that TMPRSS1 and TMPRSS3 play and TMPRSS5 may play important and specific roles in hearing.

McCoubrie JE, Miller SK, Sargeant T, Good RT, Hodder AN, **Speed TP**, de Koning-Ward TF, Crabb BS. Evidence for a common role for the serine-type Plasmodium falciparum SERA proteases: Implications for vaccine and drug design Infect Immun. 2007 Sep 24; PMID: 17893128

Serine repeat antigens (SERAs) are a family of secreted 'cysteine-like' proteases of Plasmodium parasites. Several SERAs possess an atypical active site serine residue in place of the canonical cysteine. The human malaria parasite P. falciparum possesses 6 'serine-type' (SERA1-5 and SERA9) and 3 'cysteine-type' (SERA6-8) SERAs. Here, we investigated the importance of the serine-type SERAs to blood-stage parasite development and examine the extent of functional redundancy amongst this group. We attempted to knockout the 4 P. falciparum serine-type SERA genes that have not been disrupted previously. SERA1, SERA4 and SERA9 knockout lines were generated while only SERA5, the most strongly expressed member of the SERA family, remained refractory to genetic deletion. Interestingly, we discovered that whilst SERA4-null parasites completed the blood-stage cycle normally, they exhibited a two-fold increase in the level of SERA5 mRNA. The inability to disrupt SERA5 and the apparent compensatory increase in SERA5 expression in response to deletion of SERA4 provides evidence for an important blood-stage function for the serine-type SERAs and supports the notion of functional redundancy amongst this group. Such redundancy is consistent with our phylogenetic analysis, which reveals a monophyletic grouping of the serine-type SERAs across the Plasmodia and a predominance of post-speciation expansion. While SERA5 is to some extent further validated as a target for vaccine and drug development, our data suggests that the expression level of other serine-type SERAs is the only barrier to escape from anti-SERA5 specific interventions.